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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/781,010	02/18/2004	Satoshi Koizumi	00766.000019.1	1988

5514 7590 08/02/2005

FITZPATRICK CELLA HARPER & SCINTO
30 ROCKEFELLER PLAZA
NEW YORK, NY 10112

EXAMINER	
WALICKA, MALGORZATA A	

ART UNIT	PAPER NUMBER
1652	

DATE MAILED: 08/02/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Advisory Action Before the Filing of an Appeal Brief	**Application No.** 10/781,010	**Applicant(s)** KOIZUMI ET AL.	
	Examiner Malgorzata A. Walicka	**Art Unit** 1652	

--The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

THE REPLY FILED 05 July 2005 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE.

1. ☐ The reply was filed after a final rejection, but prior to or on the same day as filing a Notice of Appeal. To avoid abandonment of this application, applicant must timely file one of the following replies: (1) an amendment, affidavit, or other evidence, which places the application in condition for allowance; (2) a Notice of Appeal (with appeal fee) in compliance with 37 CFR 41.31; or (3) a Request for Continued Examination (RCE) in compliance with 37 CFR 1.114. The reply must be filed within one of the following time periods:
   a) ☐ The period for reply expires _____ months from the mailing date of the final rejection.
   b) ☒ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection.

   Examiner Note: If box 1 is checked, check either box (a) or (b). ONLY CHECK BOX (b) WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

NOTICE OF APPEAL

2. ☒ The Notice of Appeal was filed on 02 May 2005. A brief in compliance with 37 CFR 41.37 must be filed within two months of the date of filing the Notice of Appeal (37 CFR 41.37(a)), or any extension thereof (37 CFR 41.37(e)), to avoid dismissal of the appeal. Since a Notice of Appeal has been filed, any reply must be filed within the time period set forth in 37 CFR 41.37(a).

AMENDMENTS

3. ☐ The proposed amendment(s) filed after a final rejection, but prior to the date of filing a brief, will not be entered because
   (a) ☐ They raise new issues that would require further consideration and/or search (see NOTE below);
   (b) ☐ They raise the issue of new matter (see NOTE below);
   (c) ☐ They are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or
   (d) ☐ They present additional claims without canceling a corresponding number of finally rejected claims.

   NOTE: _____. (See 37 CFR 1.116 and 41.33(a)).
4. ☐ The amendments are not in compliance with 37 CFR 1.121. See attached Notice of Non-Compliant Amendment (PTOL-324).
5. ☒ Applicant's reply has overcome the following rejection(s): See Continuation Sheet.
6. ☐ Newly proposed or amended claim(s) _____ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).
7. ☒ For purposes of appeal, the proposed amendment(s): a) ☐ will not be entered, or b) ☒ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.

   The status of the claim(s) is (or will be) as follows:
   Claim(s) allowed: _____.
   Claim(s) objected to: _____.
   Claim(s) rejected: 21-33.
   Claim(s) withdrawn from consideration: _____.

AFFIDAVIT OR OTHER EVIDENCE

8. ☐ The affidavit or other evidence filed after a final action, but before or on the date of filing a Notice of Appeal will not be entered because applicant failed to provide a showing of good and sufficient reasons why the affidavit or other evidence is necessary and was not earlier presented. See 37 CFR 1.116(e).
9. ☐ The affidavit or other evidence filed after the date of filing a Notice of Appeal, but prior to the date of filing a brief, will not be entered because the affidavit or other evidence failed to overcome all rejections under appeal and/or appellant fails to provide a showing a good and sufficient reasons why it is necessary and was not earlier presented. See 37 CFR 41.33(d)(1).
10. ☐ The affidavit or other evidence is entered. An explanation of the status of the claims after entry is below or attached.

REQUEST FOR RECONSIDERATION/OTHER

11. ☒ The request for reconsideration has been considered but does NOT place the application in condition for allowance because: see the attached.
12. ☐ Note the attached Information Disclosure Statement(s). (PTO/SB/08 or PTO-1449) Paper No(s). _____
13. ☒ Other: Examiner's references, IDSs of 07/05/5 and 05/02/05.

Continuation of 5. Applicant's reply has overcome the following rejection(s): claim 21- 22 and 24-33 under 35 USC 112, 2nd, and claim 30-32 inder 35 USC 112, 1st.

The amendment After Final was filed in this Application on July 5, 2005. Claim Claims 21 and 22 have been amended. Claims 21-22 and 24-33 are pending in the application and are the subject of this Office Action.

Advisory Action

1. Rejections

1.1. 35 USC section 112 second paragraph

Rejection of claim 21, 22 and 24-33 made in the Office Action of October 28, 2004 (previous Office Action) is withdrawn, because the claims have been amended.

1.2. 35 USC, section 112, first paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

1.2.1. Biologic deposit

Claims 30 and 33 were rejected for lack of biologic deposit. Rejection of claim 30 is withdrawn, because the cell line called namalwa KJM-1 is publicly available from the ATCC (CRL-1432.

Claim 33 is rejected. The claim is directed to a method of production of a complex carbohydrate comprising first production of uridine diphosphate by yeast cells and after that using uridine diphosphate for production of complex carbohydrate by namalwa KJM 1/pAMoERSW1 cells. These cells were for the first time obtained by Inventors themselves and the only description of these cells given in the specification, in the Example 3: Production of UDP-GlcNAc is as follows: "A namalwa line KJM-1 transformed with a plasmid pAMoERSAW1 (Japanese Published Unexamined Patent Application No.181759/94", specification page 22, line 7.

Response to Applicants' arguments

In the prosecution of the parental case (amendment May 15, '03) Applicants stated the namalwa KJM 1/pAMoERSW1 cell line could be easily obtained, without undue experimentation, according to the method described by Example 2 of the Japanese Published Unexamined Patent Application No.181759/94. The sworn translation of Example 2 of the Published Application was enclosed. However, Example 2 of the JP59/94 does not enable one skilled in the art to make the namalwa KJM-1/pAMoERSW1 transformant, because the plasmid pAMoERSW1 is not enabled. Construction of said plasmid was preceded by stepwise construction of four new plasmids, which involved five previously known plasmids of unknown source. For example, the source of plasmid **pASN6** is unknown; the source of **pAGE207** and **pAMERC3Sc** was given as Example 1, 1(11) (13) of JP59/94 which is untranslated; the source of plasmids **pAGE107** and **pPMOLI** was given as JP-A-22979 and JP-A-1

63394, but the translations of these documents was not provided by Applicants. **Plasmid pAMoERSW1 is a unique DNA construct that was prepared by Inventors; it is not prepared routinely. Only Inventors know its sequence and restriction map. Thus, the claim remains rejected for lack of biological deposit.**

Applicants current positions is,

> "In response copies of those references **[which ones?]** are enclosed and are identified on the enclosed Form PTO-1449 (attached at Tab A) together with JBC, discussed as footnote 1. As to whether or not initial production of the plasmid is simple or not for the inventors who prepared it (c.f., page 8, line 8 of the Office Action) such inquiry is off- point; even if the initial preparation was obvious, the procedure is now well characterized, even if a considerable amount of work is involved. *Ex parte Forman, 230 USPQ 546 (PTO Bd. Pat. App. Intf. 1986)*", **current** REMARKS, the paragraph bridging page 8 and 9.

This argument of Applicants is not persuasive because none of papers enclosed in the IDS of May 2, 2005 or July 5 2005 discloses plasmids **pASN6**, **pAGE207, pAMERC3Sc, pAGE107** and **pPMOLI.**

In summary, plasmid pAMoERSW1 **is unique,** publicly not available, therefore

claim 33 is rejected.

1.2. 2. Lack of written descripton

The amended independent claims 21, 22, and dependent claims 24-33 remain rejected.

Independent claims 21 and 22 are directed to a process for producing a uridine diphosphate sugar and uridine diphosphate sugar plus complex carbohydrate by a treated yeast cell, wherein the cell is

1) any surfactant–treated cell,

2) any solvent-treated cell,

3) any enzyme-treated cell.

The claims are directed to use of genera 1) - 3) of treated yeast cells. To use the invention as claimed, the treated cell has to contain the necessary enzyme(s), i.e. it has to contain all proteins produced by cell, thus including the enzyme necessary for performing the method of synthesis of a uridine diphosphate sugar. Applicants do not instruct in details how to treat a yeast cell with a surfactant, solvent or enzyme so that a

surfactant–treated cell,

solvent-treated cell, and enzyme-treated cell

still contains the enzymes necessary for synthesis of uridine diphosphate sugar.

The specification teaches on page 12 examples of the surfactant and organic solvents to be used to obtain surfactant–treated cell, solvent-treated cell, and, however the open list of the chemicals (what else should be included or excluded from the list) to

be used is not a method of obtaining surfactant–treated cell, that are the product to be used in the claimed method. Thus the products are not sufficiently described.

Furthermore, the specification is silent about any enzyme suitable for treatment of yeast cell that after treatment are to be used in the claimed method. Is the Applicants intention to use for example proteins K that will destroy all proteins in the cell? This is a complete lack of written description.

In conclusion, one skilled in the art is not convinced that applicants were in possession of the claimed invention at the time the application was filed.

Claims 30-33 were rejected in the previous Office Action as directed to a method of producing complex carbohydrate, wherein in the method COS7 and kamala KJM-1 cells transformed with a plasmid comprising DNA encoding β1, 3-galactosyltranferase or β1, 3-galactosyltranferase from human melanoma WM266-4, or the kamala KJM-1/ pAMoERSW1 cell are used.

Rejection of claims 30-32 is withdrawn because Applicants arguments (Remarks, page 9, second paragraph) are found persuasive.

Rejection of claim 33 is not withdrawn, because namalwa KJM-1/pAMoERSW1 is not described. See the above rejection for lack of biologic deposit.

1.2.2. Scope of enablement

Claims 21,. 22, 24-33 remain rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for production of uridine diphosphate

sugar by dried *S. cervisiae* or *Kluyveromyces cells*, and production of complex carbohydrate by commercially available or produced by transformed cells β1,3-galactosyltranferase which is commercially available or produced by transformed cells does not reasonably provide enablement for production of uridine diphosphate sugar and complex carbohydrates by:

1) any surfactant–treated cell,

2) any solvent-treated cell, and

3) any enzyme-treated cell,

wherein the species of genera 1) - 8) are capable of producing a uridine diphosphate sugar from a nucleotide precursor selected from the group consisting of orotic acid, uracil, orotidine and uridine and sugar or/ and are capable of producing a complex carbohydrate from the uridine sugar and a precursor of complex carbohydrate.

The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims. The scope of the claims encompasses of genera 1)-3). As stated above in rejection for lack of written description, the specification is silent as to what particular species of the subgenera 1)-3) are suitable to make the invention.

The specification does not provide any guidance or examples of detailed methods of treatment of yeast cells with any surfactant, any solvent and any enzyme, so that treated cells undamaged and capable of producing uridine diphosphate sugar form a nucleotide precursor selected from the group consisting of orotic acid, uracil, orotidine

and uridine and sugar or/and are capable of producing a complex carbohydrate from the uridine sugar and a precursor of complex carbohydrate.

One skilled in the art concludes that Applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claim. Thus, the experimentation left to those skilled in the art is improperly extensive and undue.

1.3. 35 USC section 103

Claims 21, 24 and 25 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Caputto et al. (Isolation of the Coenzyme of the Galactose Phosphate-glucose Phosphate Transformation, J. Biol. Chem. 1950, 184, 333-350,) in view of the common knowledge in the art for the reasons explained in the previous Office Action.

Response to Applicants' arguments

Traversing this rejection Applicants argue current REMARKS, page 10,

"Orotic acid uracil, orotidine and uridine are compound which become UDP-glucose precursors on the metabolic pathways. However, they are not metabolized only for the biosynthesis of UDP-glucose" and further "Caputto neither teaches nor suggests that a sugar nucleotide can be efficiently produced by yeast using orotic acid, *etc.* Moreover, such production of the sugar

nucleotide was not common knowledge at the time the present invention was made. It the Examiner disagrees, Applicants respectfully request that they be provided with a reference showing the same, " current REMARKS, page 10.

Applicants' argument has been fully considered but is found not persuasive for the following reasons.

1. Although orotic acid uracil, orotidine and uridine are compounds that are not metabolized only for the biosynthesis of UDP-glucose that does not change the fact that they **ARE USED FOR BIOSYNTHESIS OF UDP-GLUCOSE;** see Tab B with the highlighted pathway from orotic acid to UTP. UTP is a precursor to synthesis of UDP-glucose. As shown in the enclose copy of page 804, Fig. 26-9 of Biochemistry, by Voet and Voet, Second Edition, 1995, orotic acid is a direct substrate for production orotidine monophosphate, which, in turn, is a direct substrate for synthesis of uridine monophospate. Uridine monophophate is phosphorylated, and as uridine triphosphate (UTP) is the substrate for UDPglucose or other uridine diphosphate sugar. Synthesis of UDP glucose from UTP and glucose- phosphate has been known for more than half a century now; see the enclosed page 491 from the quoted handbook of biochemistry. The mechanism of the synthesis was revealed by Luis Leloir in 1950. The enzyme which synthesizes UDPglucose is called UDP-glucose-pyrophosphorylase. Because the synthesis of UTP from orotic acid, uracil, orotidine and uridine was a common knowledge at the time the invention, the inventors were aware that supplementing

medium in these precursors would improve efficiency of UDPsugar production. In summary, production of UDPsugar by yeasts was very well known at the time of invention, i. e. it was obvious.

Claims 21, 24, and 25 are also rejected under 35 U.S.C. 103(a) as being unpatentable over review by Herscovics et al. Glycoprotein biosynthesis in yeast, FASEB J. 1993, 7, 540-550), in view of common knowledge in use of S. cerevisiae in biotechnological processes. The reasons for rejection were explained in the previous Office Action.

Response to Applicants' arguments

On page 11 of their REMARKS Applicant state,

> "Herscovic suggests, but not demonstrates that *S. cerevisiae* may biosynthesize UDP-GlcNAc intracellularly based on the sugar chain structure. Also as described, above production of sugar nucleotide using orotic acid, etc. was not common knowledge prior to Applicants' invention."

Applicants' opinion has been fully considered but is found not persuasive for the following reasons. Although Herscovic in her monography on glycoproteins in yeast synthesis does not demonstrate that S. cerevisiae synthesize UDP-GlcNAc, her statement, page 541, left column, under SYNTHESIS OF SUGAR DONORS

"Similarly, a mutant that requires glucosamine for growth was used to isolate the GAF1 gene encoding the amidotransferase responsible for the synthesis of glucosamine-6-P (17), which is essential for UDP-GlcNAc formation (see Table 1)." is a statement of the fact very well known in the art for tens of years. If yeast cell did not synthesize UDP-GlcNAc it would not have had cell wall; see Fig 12.22, in the enclosed copy of page 456 from a handbook of biochemistry by Zubay, published 1986. The direct evidence is provided by for example, by an article by Yamamoto 1980, dealing with inhibition of UDP-N-acetylglucosamine pyrophosphorylase from backer's yeast, i.e., *S. cerevisiae*; the abstract enclosed. The enzyme is classified as EC2.7.7.23 and synthesizes UDP-GlcNAc; a relevant page of Enzyme Nomenclature 1992 are enclosed.

As to the synthesis of sugar nucleoide using orotic acid, it was obvious as discussed above.

Claim 22, 24, 25, 27, 29 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Tochikura et al. (Sugar Nucleotide Fermentation by Yeast, Ferment. Technol. Today, 1972, 463-471; Proc. IVth Int. Ferment. Symp., copy enclosed), further in view of Ichikawa et al. Expression cloning of a cDNA for human ceramide glucosyl transferase that catalyzes the first glycosylation step of glycosphingolipid synthesis, Proc. Natl. Acad. Sci. USA, 1996 (May) pp. 4638-4643 and in view of the common knowledge in the art. The rejection was explained in the previous Office Action.

Response to Applicants' argument

Applicants emphasize, "Tochikura produce UDP-glucose only using UMP as a precursor, and does not disclose or suggest producing UDP-glucose using orotic acid, uracil orotidine or uridine precursor", REMARKS, page 11.

As discussed above, using orotic acid, uracil, orotidine or uridine in the medium in which yeast is growing and producing UDPglucose is obvious over basic knowledge in biochemistry. Claims 22, 24, 25, 27, 29 are rejected.

3. Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Malgorzata A. Walicka whose telephone number is (571) 272-0944. The examiner can normally be reached on Monday-Friday from 10:00 a.m. to 4:30 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapura Achutamurthy, can be reached on (571) 272-0928. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should

you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Malgorzata A. Walicka, Ph.D.

Art Unit 1652

Patent Examiner

REBECCA E. PROUTY
PRIMARY EXAMINER
GROUP ~~1800~~ 1600